

# Expert Opinion

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## The case for pathogen-specific therapy

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At the beginning of the twenty-first century, the treatment of microbial diseases is increasingly complicated by drug resistance, the emergence of new pathogenic microbes, the relatively inefficacy of antimicrobial therapy in immunocompromised hosts, and the reemergence of older diseases, often with drug-resistant microbes. Some of these problems can be traced to the switch between pathogen-specific antibacterial therapy and the nonspecific antibacterial therapy that followed the transition from serum therapy to modern antimicrobial chemotherapy. The widespread availability of cheap, effective, nontoxic wide-spectrum antibacterial therapy for almost 75 years fostered a culture of therapeutic empiricism that neglected diagnostic technologies. Despite unquestioned lifesaving efficacy for individuals with microbial diseases, the use of broad-spectrum antimicrobials was associated with fungal superinfections and antibiotic-associated colitis, helped to catalyze the emergence of resistance, and is now tentatively associated in the pathogenesis of certain chronic diseases, including atopy, asthma and – perhaps – certain forms of cancer. This article briefly reviews these trends and suggests that the current strategy of nonspecific therapy is fundamentally unsound because it damages the microflora and – consequently – the human symbiont. The essay argues for the development of immunotherapy and pathogen-specific therapies, especially with regard to bacterial and fungal diseases, and suggests possible routes to that future.

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### 1. The problematic status quo

Current antimicrobial therapy is largely pathogen-specific for viral diseases and nonpathogen-specific for bacterial, fungal, and parasitic diseases [1]. Although some of the latter diseases are sometimes treated with pathogen-specific drugs, such as the use of isoniazid for tuberculosis, the overwhelming majority of compounds targeting bacteria, fungi, and parasitic diseases have activity against multiple microbes. Furthermore, these compounds target both pathogenic and nonpathogenic microbes. This current antimicrobial paradigm is currently in use at a time of significant upheaval in the therapy of microbial diseases, which is the only field of medicine in which one can argue that therapeutic options have declined over time. For example, in the 1950s Jawetz noted that the then currently available antimicrobial drugs were satisfactory for the treatment of bacterial diseases [2]. However, in recent years the field of infectious diseases has seen dramatic increases in antimicrobial resistance, an increasing prevalence of bacterial and fungal superinfections in treated individuals, a relatively low therapeutic efficacy of antimicrobial therapy in individuals with impaired immunity, the emergence of new infectious diseases, and the reemergence of older microbial diseases, often with highly resistant microbes such as XDR-Tb. Given this status quo, it behooves us to ask the questions: How did we get here? What are the consequences

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of the choices made then and now? Can we do better and how do we get there?

### 2. How did we get here?

Effective antimicrobial therapy can be dated to the introduction of serum therapy in the 1890s, which, for the first time, provided physicians with the ability to intervene and cause a favorable outcome for an infectious disease. Serum therapy was developed against numerous bacterial and viral diseases, including pneumococcal pneumonia, meningococcal meningitis, erysipelas, anthrax, and measles (for reviews, see refs [3-5]). The heyday of serum therapy was the 1930s, but the modality was rapidly abandoned because serum could not compete with small-molecule antimicrobial therapy, such as sulfonamides and penicillin, with regard to price, stability, ease of use, and (low) toxicity. For some diseases such as meningococcal meningitis, small-molecule antimicrobial therapy was clearly more effective than serum therapy; however, for pneumococcal pneumonia the difference in efficacy was less clear. In addition to serum therapy, the few other therapies available (e.g., quinine for malaria, salvarsan for syphilis, optochin for pneumococcus, and phage therapy) were all pathogen specific. In a prior essay [6], I argued that the time of serum therapy and the subsequent era of therapy with small molecules constituted the two first ages of antimicrobial therapy. When viewed through the prism of microbial specificity, the greatest difference in the therapeutic approach between the first and second ages of antimicrobial therapy was a switch from pathogen-specific to nonspecific therapy with regard to antibacterial therapeutics. In this essay, I argue that this change was to have enormous implications, which are root causes for some of the problems we face today.

In evaluating the therapeutic paradigm for microbial diseases, it is worthwhile contrasting it with the therapy of cancer. Like therapy for infectious diseases, the treatment of tumors has relied heavily on antibiotics made by microorganisms; adriamycin, actinomycin D, bleomycin etc. are all microbial products. Like antimicrobial antibiotics, these antimetabolite antibiotics are each nonspecific in the sense that they are cytotoxic to multiple tumors. However, unlike most antimicrobial antibiotics, these agents have tremendous toxicity for the host and, consequently, are never used empirically. Hence, oncology practice has placed great emphasis on diagnosis and in exploiting subtle pharmacological differences between these agents to enhance their therapeutic index.

In fairness to infectious diseases, it is noteworthy that the temporal kinetics of microbial infections and tumorigenesis favored a more deliberate approach to diagnosis as tumors, which unlike microbes, seldom killed the host rapidly. Nevertheless, the analogy is relevant because it provides an inkling of how the practice of infectious diseases might have developed if early antimicrobials had more significant toxicity, as

evidenced by the hesitant empiric use of amphotericin b and Ara-C for fungal and herpetic diseases, respectively. Consistent with this notion, the development of the relatively nontoxic antiherpetic drug acyclovir as a replacement for Ara-C was followed with significantly greater empiric use, especially in neonates and cases of encephalitis. Similarly, the introduction of low-toxicity azoles and echinocandins as replacements for the highly toxic amphotericin b has promoted the empirical use of antifungal therapy. Hence, the advantage of low toxicity has the perverse effect of promoting empirical and inappropriate use.

In comparing the ages of antimicrobial therapy, it is clear that the change in the specificity of therapeutic agents did not affect all types of antimicrobial therapy equally. Serum therapy for viral diseases was specific and current antiviral drugs remain largely pathogen-specific, with the caveat that some drugs like acyclovir have activity against multiple herpesviruses. For mycobacterial diseases, there was no effective therapy in the preantibiotic era and most drugs that were subsequently developed (isoniazid, ethambutol, and others) were used primarily for the therapy of tuberculosis. For fungal diseases, there was no effective therapy prior to the late 1950s when amphotericin B was introduced; a compound active against most fungal pathogens and antifungal therapy has always relied on nonpathogen-specific agents. For bacterial diseases, the change from serum to small-molecule therapeutics was a revolution, as therapeutic specificity was abandoned in favor of agents with increasingly greater spectrum of antimicrobial activity. However, what made the switch from pathogen-specific to nonpathogen-specific therapy so significant with regard to antibacterial therapy is that the human host is a symbiont, with microflora consisting mostly of desired commensal bacteria. By contrast, there are no known desirable commensal viruses and the known fungal flora is limited to a few fungal species where *Candida* spp predominate. Unlike bacteria, a beneficial function has not been demonstrated for the host-associated fungal microflora. Hence, the use of nonspecific bacterial therapy carried an inherent potentially detrimental effect in damaging the associated bacterial microflora, and thus the human symbiont.

### 3. The consequences of nonspecific antimicrobial therapy

The nonspecificity of antibacterial, and to a lesser extent antifungal, therapies was to have profound consequences on the practice and outcome of infectious diseases that reverberate to current times. The availability of nonspecific antibacterial therapies with broad spectrum and low toxicity allowed physicians to rapidly treat many infectious diseases without a need for a microbial diagnosis. For individuals with bacterial diseases, such therapy was often lifesaving. However, the ability to effectively treat many diseases safely without making a diagnosis deemphasized diagnostic clinical microbiology and fostered a culture of empiricism. For

example, the diagnosis of pneumococcal pneumonia with the identification of the offending serotype took approximately 6 – 8 h in the 1930s and used the mouse peritoneal infection assay followed by typing with rabbit type-specific serum. This methodology was developed to rapidly ascertain the presence and serotype of pneumococcus in sputum because the efficacy of serum therapy depended on matching the bacterial serotype with the specificity of the antiserum. Despite the problems in unequivocally diagnosing pneumonia from sputum, this approach was successful for selecting therapeutic sera and supported the use of serum therapy. However, the introduction of penicillin and later antimicrobial drugs made the test much less relevant and it was abandoned as a diagnostic tool. Currently, a definitive diagnosis of pneumococcal pneumonia is possible only when accompanied by bacteremia, information that requires 48 h. For fungal diseases, a full embrace of empiric therapy was checked by the toxicity of amphotericin b, but by the late 1990s, the availability of relatively nontoxic azole and echinocandin-type drugs had ushered greater empiric use. By contrast, for conditions that required specific therapy, such as viral and mycobacterial diseases, the practice ethos supported continued emphasis on diagnostic identification of the causative microbe.

For bacterial and later fungal diseases, the availability of relatively nontoxic broad-spectrum therapy contributed to the emergence of resistance among both targeted and nontargeted microbes. Although specific therapy can also elicit resistance, as witnessed by the emergence of isoniazid-resistant *Mycobacterium tuberculosis*, only nonspecific therapy can elicit resistance among nontargeted microbes such as common inhabitants of the microflora. Furthermore, only nonspecific therapy can damage the microflora to create alterations that foster the emergence of usually commensal microbes such as *Candida* and *Enterococcus* spp, first as major pathogenic microbes and then as drug-resistant pathogenic microbes. Consequently, the discipline of infectious diseases may be the only specialty of medicine where previously effective therapeutic options have to be abandoned because of drug resistance creates obsolescence.

Another consequence of nonspecific antibacterial and antifungal therapy was damage to the human symbiont. There is rapidly accumulating evidence that the human microflora is established early in life through complex steps and that there are individual differences in microbial species composition, a fact that could reflect differences in the timing of acquisition or modulation by the host immune system. The microbial flora is essential for development of the immune system, helps digestion, provides numerous nutrients including vitamins, and protects the human host by niche-denial to more pathogenic microbes. There is conclusive evidence that damage to the microflora by nonspecific antibacterial therapy can translate into antibiotic-associated colitis and fungal diseases such as oral thrush and candidal vaginitis. However, there are ominous signs that nonspecific

antimicrobial use might translate into certain chronic diseases such as atopy [7], asthma [8], and even some types of cancer [9], possibly by altering the development of the immune system in childhood and/or affecting metabolites produced by the microflora. In this regard, it is noteworthy that there is a temporal association between widespread antimicrobial use and the increase in immunoreactive diseases such as allergies and asthma, although it is premature to conclude causality as there may be confounding variables [10]. Nevertheless, the available evidence does provide reason for concern.

In summary, the development of effective, nontoxic, nonspecific antibacterial and antifungal therapy has had great consequences, some positive and some negative. Positive consequences include a significantly enhanced capacity to treat bacterial and fungal diseases early and effectively, which has translated to reduced mortality. Furthermore, the ability to treat early, safely, and without knowledge of the causative microbe has created a permissive environment for the development of complex surgeries, aggressive chemotherapy for tumors, and organ transplantation, procedures that would have unacceptable mortality without such drugs. However, the same approach has also created a culture of empiricism that promoted antibiotic use, which in turn selected for resistance in targeted and nontargeted microbes, promoted the phenomenon of superinfection and damaged the symbiont with consequences that are only now beginning to be understood. In this regard, empiricism was a practice largely dictated by clinical findings and historical probability that essentially rejected causality in favor of associations.

#### 4. Can we do better and how to get there?

Of course we can do better. Even for the short historical time that effective antimicrobial therapy has been available it is clear that the effectiveness of therapy and diagnosis has fluctuated with time. In a previous essay [6], I argued that we are in the throes of a major paradigm shift that will usher in the third age of antimicrobial therapy. This age can be envisioned as an equilateral triangle with pathogen-specific therapy, greatly improved diagnostics, and immunotherapy at each apex. Nonspecific therapy will always have a role for the treatment of polymicrobial diseases and to insure proper coverage in individuals with fulminant disease but its use could be limited by the combination of rapid diagnostics and pathogen-specific drugs. Even for such polymicrobial diseases as abdominal sepsis originating from a ruptured viscus there is evidence that damage is caused by only a few microbial species and their identification would permit employment of pathogen-specific drugs. In this age, immunotherapy, whether with large molecules, such as antibodies or small-molecular-weight immunomodulators, would have co-equal status with therapies designed to directly kill or inhibit the microbe. Although this author believes that third-age therapeutics will arrive in the twenty-first century,

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significant scientific, economic, and behavioral hurdles must be overcome for the realization of this vision.

On the scientific front, drug discovery would have to move from trying to identify common therapeutic pathways among phylogenetically distant bacteria to exploiting differences in physiology and virulence mechanisms and/or to augmenting host mechanisms that promote microbial clearance, which, interestingly, are nonspecific. This formidable task is made even more difficult by the economics of antimicrobial drug discovery. As for other diseases, the economics of drug development is a function of the prevalence of the disease, which dictates market size. However, in antimicrobial drug discovery this formula is further modified by the fact that the market size is directly proportional to the width of the drug antimicrobial spectrum. Given the cost of drug development, the economics are stacked against pathogen-specific drugs in favor of broad-spectrum drugs. One caveat in this analysis is that drug resistance can disproportionately shorten the useful life of broad-spectrum drugs and that the emergence of resistant microbes can in itself create new market opportunities. For example, the emergence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA) creates a niche such that a new staphylococcal-specific drug active against methicillin- and possibly vancomycin-resistant isolates would probably be developed clinically if available. The use of pathogen-specific drugs would necessitate advances in diagnostics to provide rapid and accurate information to support their use, and this would require new investments in research and laboratory assays. Finally, physicians would have to change their approach to patients with presumed infectious diseases, emphasizing the need for diagnosis to select appropriate therapy in an echo to the practices of physicians in the age of serum therapy.

Perhaps the hurdles are so high that pathogen-specific therapy is only in the far horizon. If that is the case, there are concrete actions that can be taken in the present to slow the spread of drug resistance and damage to the human microbial flora. For example, educational campaigns aimed at physicians and the general public can promote more prudent use of antimicrobial drugs. At a political level, policy makers should be made aware of the economic and regulatory hurdles that slow the development of rapid diagnostic tests and pathogen-specific drugs. However, perhaps things can change more rapidly than one can anticipate. Certainly, if future research was to associate disturbances in the microflora with such chronic diseases as asthma, atopy, and cancer, this would create tremendous medical and legal disincentives in the use of nonspecific microbial therapy. Another powerful force could be the categorization of such complications of

broad-spectrum therapy as *C. difficile* colitis and candidiasis as medical errors, which would be followed by aversion of third-party payers for hospital and physician reimbursements. At the same time, economic incentives for the development of pathogen-specific therapy by industry could be created by linking the patent protection time of antimicrobial drugs to the width of the antimicrobial spectrum and inclusion of narrow-spectrum drugs as orphan drugs. For example, patent policy could be amended such that narrow-spectrum drugs with small markets enjoy much longer patent protection than broad-spectrum drugs. Although in 2009 a revolution in the antimicrobial therapeutic paradigm seems distant, it is worth noting that only a generation ago smoking was widely permitted and accepted in most public places. For smoking, it was the realization that second-hand smoke was dangerous that catalyzed the creation of smoke-free environments in most public places. Perhaps increased awareness of the consequences of long-term damage to the human flora will have a similar catalytic effect in promoting pathogen-specific antimicrobial therapies.

The re-introduction of pathogen-specific therapy for bacterial diseases, and its extension to fungal diseases, would require a concerted effort and collaboration between intellectual leaders in the field, industry, and government to find mechanisms that would promote and encourage the development of such drugs. There are indications of movement in this direction. A recent report by the Institute of Medicine recommended 'development of strategies that will selectively target pathogenic organisms while avoiding targeting the host and beneficial or benign organisms', which in other words is pathogen-specific therapy [11]. Several therapies narrow-spectrum are currently in development, for example, the renewed interest in phage therapy, monoclonal antibody therapies, and drugs aimed primarily at targeting highly resistant bacteria. However, the task of refocusing antibacterial and antifungal therapy to pathogen specificity is too great for any individual party and cooperation from industry, government, and the medical community will be needed to effect change. There is an acute need for an economic model that would allow the development and use of pathogen-specific drugs. Despite these hurdles, it is clear that pathogen-specific therapy makes sense and, given that the current nonspecific strategies are increasingly bankrupt, it behooves all parties to begin a dialogue on how to get there, and get there sooner than later.

### Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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